U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION



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MEDICAL DEVICES ADVISORY COMMITTEE
CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY
DEVICES PANEL

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FRIDAY
MARCH 24, 2000

The Panel met in the Main Conference Room at 9200 Corporate Boulevard, Rockville, Maryland, at 9:30 a.m., Martin H. Kroll, M.D., Chairperson, presiding.

PRESENT:

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| MARTIN H. KROLL, M.D. | Chairperson |
| BARBARA R. MANNO, Ph.D. | Member |
| NADER RIFAI, Ph.D. | Member |
| ARLAN L. ROSENBLOOM, M.D. | Temporary Voting Member |
| JEFFREY A. BRINKER, M.D. | Temporary Voting Member |
| STEPHEN CLEMENT, M.D. | Temporary Voting Member |
| PHILIP C. COMP, M.D., Ph.D. | Temporary Voting Member |
| JAMES EVERETT, M.D., Ph.D | Temporary Voting Member |
| CASSANDRA E. HENDERSON, M.D. | Temporary Voting Member |
| MILTON PACKER, M.D. | Temporary Voting Member |
| STANLEY M. REYNOLDS | Consumer Representative |
| ERIKA B. AMIRATTI, R.A.C. | Industry Representative |
| VERONICA J. CALVIN, M.D. | Executive Secretary |

SPONSOR REPRESENTATIVES:

JOHN F. BRUNI, Ph.D., Director, Clinical and Regulatory Affairs, Biosite Diagnostics

ALAN MAISEL, M.D., Professor of Medicine, UCSD

GUNARS E. VALKIRS, Ph.D. Vice President, Research and Development, Biosite Diagnostics

SPONSOR REPRESENTATIVES (continued):

KENNETH BUECHLER, Ph.D. Vice President, Research, Biosite Diagnostics

ROBERT H. CHRISTENSON, Ph.D. Director of Chemistry, University of Maryland

FDA PARTICIPANTS:

PHILIP J. PHILLIPS, Deputy Director for Science and Regulatory Policy

RUTH CHESLER, B.S.,M.T.(ASCP) Scientific Reviewer, Division of Clinical Laboratory Devices, Office of Device Evaluation

STEVEN I. GUTMAN, M.D., MBA Director, Division of Clinical Laboratory Devices

PUBLIC COMMENT:

GARY ROBINSON, Igen

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

(9:32 a.m.)

DR. KROLL: Good morning. I am Martin Kroll and I am the Acting Chair of this panel. What I would like to do is call this panel meeting to order. I would like to turn things over to Veronica Calvin.

MS. CALVIN: Good morning and welcome to this meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel. Before we begin today's agenda, I will provide brief summary minutes from the last panel meeting.

The Clinical Chemistry and Clinical Toxicology Devices Panel met on December 5 and 7, 1999. On December 6 the panel discussed the glucowatch automatic glucose biographer manufactured by Cygnus, Incorporated, and voted unanimously recommending approvable with conditions.

On December 7 the panel provided advice and recommendations on general issues concerning over the counter vaginal pH devices. More information on this meeting can be found on our web site at www.fda.gov/cdrh/ccctdp.html.

Today the committee will discuss, make recommendations, and vote on a premarket approval

application for a peptide type test indicated as an aid in the diagnosis of congestive heart failure.

I would like to note for the record that Dr. Martin Kroll, as he has stated, has agreed to serve as Chair for the duration of this meeting. He is the Director of Clinical Chemistry at the Dallas VA Medical Center.

I would also like to note that Mr. Stanley Reynolds from the Microbiology Devices Panel is substituting for our Consumer Rep Davida Kruger, and Ms. Erika Ammirati, from the Immunology Devices Panel and our former Industry Rep, is serving as Industry Rep for today.

We are also pleased to have a representative from the Hematology and Pathology Devices Panel, the Circulatory Devices Panel, and the Cardiovascular and Renal Drugs Advisory Committee.

I will now read the Conflict of Interest Statement. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety. The conflict of interest statutes prohibit special Government employees from participating in matters that could affect their or their employer's financial interest.

To determine if any conflict exist, the agency reviewed the submitted agenda and all financial interest reported by the committee participants. The agency has no conflicts to report. In the event that the discussions involve any of the products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

I will now read two Appointment to Temporary Voting Status Memos and, please, I apologize for the redundancy. "Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27, 1990, and as amended August 18, 1999, I appoint the following individuals as members of the Clinical Chemistry and Clinical Toxicology Devices Panel for this meeting on March 24, 2000. Jeffrey A. Brinker, M.D., Stephen Clement, M.D., Philip C. Comp, M.D., Ph.D., James Everett, M.D., Ph.D., Cassandra E. Henderson, M.D.

For the record, these individuals are special Government employees and consultants to this panel or other panels under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. Signed, David W. Feigel, Jr., M.D., M.P.H., Director, Center for Devices and Radiological Health.

"Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27, 1990, and as amended August 18, 1999, I appoint Milton Packer, M.D. as a voting member of the Clinical Chemistry and Clinical Toxicology Devices Panel for this meeting on March 24, 2000.

He is a special Government employee and a member and chair of the Cardiovascular and Renal Drugs Advisory Committee. He has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting. Signed, Linda A. Sudam, DPA, Senior Associate Commission."

I'll now turn the meeting back over to Dr. Kroll who will have the panel members introduce themselves.

DR. KROLL: Thank you. What I would like to do now is have each panel member introduce

themselves, tell us their affiliations, and also tell us their status on the panel. Why don't we start to my right here.

DR. RIFAI: I'm Nader Rifai. I'm Associate Professor of Pathology at Harvard Medical School and the Director of Clinical Chemistry Lab at Children's Hospital. I'm a voting member on this panel.

DR. ROSENBLOOM: I'm Arlan Rosenbloom, Distinguished Professor Emeritus in Pediatrics, University of Florida and Assistant Medical Director of Children Medical Services and I'm a voting member of the panel.

DR. HENDERSON: I'm Cassandra Henderson. I am an Associate Professor of Obstetrics and Gynecology in the Division of Maternal Fetal Medicine at Albert Einstein College of Medicine in the Bronx. I'm also a Medical Director of the MIC - Women's Health Services Center in New York City. I'm a temporary voting member.

DR. BRINKER: I'm Jeff Brinker. I'm Professor of Medicine and Radiology at Johns Hopkins. I'm an Interventional Cardiologist and temporary voting member.

DR. MANNO: I'm Barbara Manno. I am Co-

Director of the Clinical Toxicology Laboratory and Professor of Psychiatry at the Louisiana State University Health Sciences Center in Shreveport, Louisiana.

DR. GUTMAN: I'm Steven Gutman. I'm the Director of the Division of Clinical Laboratory Devices.

MR. REYNOLDS: I'm Stanley Reynolds. I'm supervisor of Immunology and Virology, Commonwealth of Pennsylvania, Bureau of Laboratories, and I am the Consumer Representative on the panel.

MS. AMMIRATI: Good morning. I'm Erika Ammirati. I'm an independent consultant with Clinical Trials and Regulatory Affairs. I'm subbing today as the Industry Rep to this panel.

DR. EVERETT: I'm James Everett, Medical Director of Madison Memorial Health Care in Madison, Florida. I'm a temporary voting member of this panel.

DR. CLEMENT: Steve Clement, local person here, Georgetown University, Associate Professor, specialty in Endocrinology, and permanent voting member.

DR. PACKER: I'm Milton Packer, Professor of Medicine, Columbia University, Director of the Heart Failure Center there, and also Chair the Cardio-

Renal Drugs Advisory Panel.

DR. COMP: I'm Philip Comp, University of Oklahoma. I'm a Professor of Medicine, Adjunct Professor Pathology. I'm here as a temporary voting member.

DR. KROLL: Thank you. Now I would like to turn this meeting over to Philip J. Phillips, Deputy Director for Science and Regulatory Policy.

MR. PHILLIPS: Good morning, Dr. Kroll and other distinguished members of the panel. Back in November of 1997 President Clinton signed into law what many people consider to be one of the most significant pieces of legislation in the history of the FDA and that is the FDA Modernization Act of 1997.

It is a rather complex piece of legislation. I would encourage anybody who is really interested in a lot of the details to go to the FDA web site. You can go under FDAMA and you'll find it's just a wealth of information about the law and how we have implemented the various provisions.

Today we are here to talk about what is called the least burdensome provisions of the FDA Modernization Act of 1997. I hope that you are going to find this rather interesting and useful as we go into the future.

As far as today's presentation, it should be relatively short, concise, and to the point. I plan on talking about the specific references to the least burdensome requirements that are in the law. I'll talk about some of the things that we've done to actually implement this particular provision, as well as some of the mechanisms that we recognize to date that may lessen some of the regulatory burden associated with what we do.

As far as the references to the actual least burdensome provisions, you'll find them in Section 513. There are actually two references to the words "least burdensome." One is in 513(a) and the other is in 513 (i). We'll look at each one of these in just a little bit more detail.

Under Section 513(a) let me just read the one sentence that I think is the most important that's in the law. It says, "The Secretary shall consider in conjunction with the applicant the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.

This specifically refers to premarket approval or PMA requirements. I think it's important for you to recognize that because the next overhead

when we go to it, we'll talk about 510(k) requirements.

But, again, this is what it is that the Congress has instructed us to do. You can imagine it's a relatively difficult job because what does least burdensome mean? That's what it is that we are going through right now in conjunction with a lot of different interested groups to try to figure out exactly what least burdensome means in the context of FDA regulation.

The next section 513(i) deals with premarket notifications or 510(k)s. Let me just say that I think it is relatively unusual that advisory panels get involved in 510(k) evaluations but it does happen on occasion. Most of what you do as advisory committee members is deal with premarket approval applications. The previous slide is probably more applicable to panel activities than this but, nevertheless, on occasion we do bring 510(k)s for review by panels.

Let me just again read just the one sentence that I think is the one that is most of the points. "In making such requests -- this is requests for additional information -- the Secretary shall consider the least burdensome means of demonstrating

substantial equivalents and request information accordingly." Again, those are the two references to the words least burdensome that now appear in our amended law.

One thing that is absolutely imperative that everyone understand is that FDAMA did not change the standard for premarket clearance or approval. We talk about premarket approval. We're talking about reasonable assurance of safety and effectiveness. The words least burdensome did not change that standard. When we talk about 510(k)s we're talking about substantial equivalents and, again, the law did not change that standard either.

As far as the actual implementation, let me just give you a little bit of a brief overview about what we've done since November of 1997. There was an open public meeting that we had in this very room just a little over a year ago. It was on January 4. It was very well attended.

There were a lot of advisory committee members that were actually in attendance in that meeting, as well as professional associations and industry groups and consumer groups that participated in the discussion of the term least burdensome.

After that there's been some internal

communications that we have had. We've actually tried to put on some training for some of our reviewers inside. A little bit more detail than what we are going through this morning but, nevertheless, it's along the same type of format.

There was also a draft guidance document that was released last fall. It was entitled, "Evidence Models for the Least Burdensome Means to Market." There was a Federal Register notice. That document still does appear on the web and this is the actual web address for this document.

The comment period for this document closed November 30 of last year so November 30, 1999. We are still in the process of actually evaluating some of the comments that came in to determine how we are going to proceed into the future, whether we are going to redraft this document or whether we are going to start with a completely different document. We are still in the process of actually looking at this a little bit closer.

As part of that guidance document, there was also an industry proposal that came in and it was from the Least Burdensome Industry Task Force. This is represented by a very wide breath of representatives from the device industry and from

various trade associations around the country.

The proposal came in March of 1999 and we actually incorporated that particular proposal as Appendix D in the guidance document that I just talked about. It was after the exact same comment period so the comment period ended November of last year and again we are going through and evaluating the comments on our guidance as well as the industry guidance.

As far as a definition of least burdensome, we've come up with what we'll call an inner definition. It's not final until we figure out exactly how we are going to proceed with developing guidance or more clear instructions on this particular provision. We've said that least burdensome is really a successful means of addressing a premarket issue that involves the smallest investment of time, effort, and money on the part of the submitter and the FDA.

Keep in mind successful means that you've met that statutory criteria. You've shown reasonable assurance of safety and effectiveness or you've shown substantial equivalents. We're not talking about cutting any corners here that don't get us to the statutory requirement for our clearances.

Some suggest that the term least burdensome requires a change in FDA culture. Well,

you know, maybe it does require a cultural change but I think that certainly what it does is requires us all to at least get on the same page when we regulate all the different products that we regulate as medical devices.

I think that it's very important that we all recognize that there are multiple approaches to satisfying regulatory requirements. There is no one way in order to show that a product is safe and effective or substantial equivalent. What we have to have is a more open mind.

It's important for us to be able to communicate and collaborate and also, and I've underlined this, compromise in the interest of public health. The reason I say that, and sometimes I get people's attention when they hear compromise in the same context as public health, but we all realize that we can design the most perfect protocols but sometimes they are very difficult for us to implement and carry out exactly as they were designed.

What we have to do is face reality to a certain extent and realize that things may not turn out exactly perfect and we are going to have to make a decision as to whether it is good enough to meet that statutory requirement of reasonable assurance of

safety and effectiveness or someone is going to have to go back and either redo a study or maybe even start completely fresh.

It's important for us to all understand that e need to follow not just the letter of law but also the spirit of the law. I think that one of the most important aspects of FDAMA is that it really did build in the requirement for us to interact with all interested parties. That's not just the regulated industry but all interested parties.

That's prompted the agency to put on a series of stakeholder meetings all across the country where we bring in people from consumer groups and professional societies to discuss different aspects of the agency. It's also important for us all to start realizing that time, effort, and money is an important consideration in our decision making.

Least burdensome, as I said before, the standard has not changed but also I don't think that least burdensome means that it's in any way a compromise of scientific integrity. I think that they can go hand in hand. I think we all recognize that any scientific endeavors that we undertaken are affected by the availability of resources.

Many of the people that are here today are

running departments and you realize the job that you do is going to depend to a large extent upon the resources that you're providing, either money, dollars, or people, both of those. It's very important for us to realize that.

Also, good science does include cost effectiveness and that's because we all operate under limited budgets. I think even the regulated industry when they go about showing a product is safe and effective, there are limits as to what it is that they can or are willing to spend in order to be able to show that a product is safe and effective. It is something that affects all scientific research and, again, it is something that all of need to be thinking about.

We also need to recognize that compromise is a necessity for successful research. Just as I said a moment ago, it's often difficult for us to carry out the perfect clinical study. We all realize that any studies that we do, even if they're bench studies, you find that there are problems that we run into when we start carrying out research and we have to make sure that we make appropriate adjustments and compensate for some of the difficulties that we do encounter.

Also, I think it's important that we all recognize that lessening regulatory burden may, in fact, serve to enhance scientific progress and advanced medicine. Clearly, none of us in this room or on the floors above us in the building want to over regulate products because if you over regulate products, what you do is deny access to new medical technologies to practitioners such as yourselves or to the American public.

It's very important for us to make sure that we titrate our amount of regulation just to the proper amount so that we can facilitate products getting to the market place.

I can give you a few mechanisms that we've come up with that might serve to lessen regulatory burden. Again, I think for many of you, you probably have been operating under with these same mechanisms in mind in the past so it's not something that is completely new but let me go through them.

I think we all need to make sure that our regulatory decisions are made in accordance with the relevant statutory criteria. The law is what gives us the authority to regulate products and we need to make sure that we go back and we look at the law and our regulations and we follow them to make sure that we

are meeting our statutory mandate and not going off and answering other questions that may not be strictly related to what our FDA mission is all about.

We all need to use the tools that have been provided by the FDA Modernization Act as well as some of the internal reengineering that we've gone through. The importance of this, and let me just illustrate this with just a couple of examples - exemptions. As a result of the FDA Modernization Act most Class I devices are exempt from premarket evaluation.

It's important because what that means is that we will be able to shift some of our internal resources into looking at higher priority types of products rather than continue to see the low risk types of products that we've seen hundreds of times. We don't need to look at those.

We can allow those to go to market through either general controls or special controls and we can spend our time looking at either the higher risk types of products that we often find in PMA, the more significant types of 510(k)s that involve changes in technologies and changes in indications for use.

We need to factor all of the relevant publicly available information into our decision

making. This is something that is somewhat difficult for us to do sometimes but we can't ignore the scientific progress that has already taken place.

When we see things that appear particularly in the peer review literature, we need to factor those in either to the evaluations of the applications that are coming before us, or even the development of guidance documents that we have because I think we need to make sure that the agency continues to progress with all of the scientific information that is available to us.

We need to rely on nonclinical testing for decision making whenever possible. I think as a laboratory panel I think that this is something that will probably ring true with this group more than anyone else. If you deal with actual bench testing results you can get a great deal of precision. When you start dealing with clinical results, you find that you lose some of that precision.

We can measure things at the bench, the very, very small increments. We're talking about nanometers and picoseconds. When you start dealing with clinical trials, things become a little bit more gross and that does cause some interesting issues at times.

We need to rely on conformists to recognize standards in decision making. You'll find that if we look at particularly the global economy, you'll find that all the countries around the world are putting a great deal of emphasis on trying to develop standards that apply to various different types of products, things that FDA regulates and even nonregulated products.

A tremendous amount of effort, dollars, and resources that are being put into the standards development process, we can reap a tremendous amount of benefits from having good standards as well. I think that certainly even in the laboratory area this is one where there is a lot of room for a lot of progress in developing the appropriate types of standards that will assure the safety and effectiveness of the different types of laboratory products that we regulate.

When we need clinical data, we need to consider alternatives to randomize controlled clinical trials. This is something that is important because I think we all need to recognize that the randomized controlled trial is perhaps the most difficult trial for us to conduct or for the industry to conduct.

That's not to say that that's not

appropriate at certain times for us to have a randomized control trial, but you'll find that particularly if you're dealing with devices and technologies that have been around for a long period of time, you'll find that there may be a lot of information, particularly out in the public domain that we can use for changing that study design somewhat so that we are relying upon either the literature or on nonactive controls. This is something that we need to think about very early on in the process whenever we design studies for particular types of products.

We need to use also surrogate endpoints whenever possible when we are looking at effectiveness. Again, because what we can do if we use proper surrogate endpoints is we can actually shorten the duration of some of the clinical trials so that we can get products that are safe and effective out on the market place a little bit sooner.

I think it's important for us to focus on effectiveness. Let's keep in mind one thing that I said earlier when I went through the law is that least burdensome applies to the effectiveness determinations of premarket approval applications.

What is the bottom line? I told you I

would make this short and I hope I have kept my word. I think that we all need to factor least burdensome concepts into all of our premarket activities. Again, when I address an advisory committee, generally what we're talking about is looking at premarket approval applications.

You will be involved in a lot of other different activities and we all need to think about least burdensome in virtually everything that we do whether it's development of guidance documents, or whether it's the review of a regulation, or taking a classification action with a new product or a reclassification for an old product. This is something that we all need to think about.

We also need to make sure that we remain open minded to alternative proposals for satisfying regulatory requirements. Generally in the past we've looked at the law and what we've said is that the law tells us that if we're going to find a product deficient or a study deficient or anything deficient, we're supposed to try to give suggestions for how a company can overcome those deficiencies.

I think that is still true today, but I think that we all need to go back and recognize that, again, there's not one way of satisfying a

requirement. There may be multiple ways and all this is saying is being open minded.

That is the bottom line but, you know, I think I can say one more summary statement. It's kind of interesting. You go back and you look and you see what it is that Congress has done. It's almost as if they tried to build common sense into the regulatory process. Least burdensome is something that should have always been in the forefront.

I think by actually putting the particular language into the law, it's going to require all of us to focus on this and think about it as we go about either designing studies or commenting on studies or evaluating data and marketing applications. Are there any questions?

DR. KROLL: Thank you very much. Again, if anybody has any questions for him, now is a good time to ask.

MS. AMMIRATI: I have one. I haven't been following this that closely but, as I recall, a lot of this is starting with the non-IVD types of products, more traditional devices. Those of us in IVD are sort of the lowest life form so things we get kind of trickle down. Was there an effort to sort of -- I'm sorry.

MR. PHILLIPS: I will take exception with that as well.

MS. AMMIRATI: I'm sorry. I'm saying that defensively obviously. Is that your sense that first we re starting to look at non-IVDs, more traditional devices for this?

MR. PHILLIPS: Let me just say I think that we're not in anyway trying to slight the IVD industry because in some of the discussions we've had, we've had representation from the IVD industry at the table. I think that just because of the magnitude of products that we regulate, IVD is a smaller subset. I mean, there are five other operating divisions and a lot of other different products.

I think if it appears as if we are somehow slighting the IVD industry, I don't believe that's true. I think it's just simply because of the number of products that we regulate and the fact that we are looking at all of the different products, Class I, II, and III for all operation divisions.

MS. AMMIRATI: My point wasn't to grouse. I was trying to add some humor, but because it is a subset, I think a lot of times IVDs are looked at a little bit differently and will there be two not too different sets of either guidance through the least

burdensome. What I read that we're going to wait for IVDs. We want to look at some of these other products first and that we're going to wait.

MR. PHILLIPS: I don't think we're waiting for IVDs. What I would refer you to, there is a guidance -- I won't call it a guidance document. It's a product of industry and FDA collaboration that is now on our web site. Let me just tell you how you find this. You go to the FDA web site. You can go to cdrh. You can go under fdama and there is a least burdensome page.

Right now as I speak there is one document that is appearing on that and that is one that deals with general concepts of the least burdensome provisions. This is something that we worked with with virtually all aspects of the device industry including the IVD segment.

I think what you will find is that all of those general concepts equally apply to IVDs as well as any other products. It could be that in the future we're going to have to get more specific details that apply this specifically to IVDs. I think at this time we're at such a general focus that it's really applying to all regulated products.

Okay. thank you very much.

DR. KROLL: Thank you. Any other questions for Mr. Phillips?

All right. At this time we would like to open our public hearing. Any interested persons may address the panel and present information relevant to the agenda. Our speakers are asked to state whether or not they have any financial involvement with the manufacturer of the product being discussed or with their competitor.

Also we ask at the presenter's table no one should be there unless their organization is presenting. At this time do we have anybody who would like to go ahead and make a presentation?

All right. It appears that there is no one at this time who wants to make a presentation. In the interest of time, we can actually ask the sponsor to make their presentation now. Again, they are limited to one hour.

I believe this is Dr. John F. Bruni. Why don't you go ahead and finish your introduction for us.

DR. BRUNI: My name is John Bruni. I'm the Director of Clinical and Regulatory Affairs for Biosite. I will be presenting the overall view of BNP and some of the clinical performance followed up by

Dr. Alan Maisel who is a Professor of Medicine at the University of California, San Diego, and the Director of the Coronary Care Unit and Heart Failure Program at the VA in San Diego.

Dr. Robert Christenson from the University of Maryland will be available to answer any questions regarding the analytical performance of the test should that be necessary. We also have Dr. Gunars Valkirs, Vice President of Research and Development who can answer some technical questions should there be any, and Dr. Buechler if there is anything regarding the device, any questions.

I would like to thank the FDA and the panel for taking the time to review this application of the triage B-type natriuretic peptide test. The material that I'm going to be going through today, the B-type natriuretic peptide, is also called brain natriuretic peptide for reasons that I'll explain later, or brain-derived natriuretic peptide which will also become obvious.

I tend to give an overview of BNP, the clinical performance of the product, and Dr. Maisel will be presenting the clinical use in the emergency department and the assessment of left ventricular dysfunction.

The atrial natriuretic factor was initially discovered in 1956. Prior to 1980 control of extracellular fluid volume and blood pressure regulation was through the renin-angiotensin aldosterone axis and other natriuretic mechanisms which include antidiarhetic hormone.

In 1981 deBold and others isolated atrial natriuretic peptide from the myocardium of rats. This is primary localized in the atrium. In 1988 Sudoh isolated a natriuretic peptide BNP from the brains of pigs or the porcine brain, thus the term brain derived or brain natriuretic peptide.

Sudoh also isolated in 1990 another natriuretic peptide, C natriuretic peptide from porcine brain. Since about 1980, the past 20 years, numerous physiological and pathophysiological studies regarding the significance of BNP have been performed in the assessment of the its relationship to congestive heart failure and heart function and the heart as an endocrine organ.

BNP has been shown to be associated with mortality and morbidity in asymptomatic and minimally symptomatic patients with left ventricular dysfunction. This is probably the best article I've been able to find in literature by Tsutamo, et al. in

1999.

He followed 290 patients for six years who were asymptomatic or newly symptomatic of congestive heart failure with the hemodynamics clinical characteristics in the treatment of the patients. They determined that BNP was the highest predictor of mortality in this cohort of patients.

They noted there was increase in CHF. There was correlation with pulmonary capillary wedge pressure, left ventricular ejection function, and is also elevated in acute myocardial infarction.

Their final conclusion was that is the best predictor of disease from not so advanced to advanced, thus the assessment of plasma brain natriuretic peptide is simple and cost effective and can be repeated and may be a useful addition to the standard political investigation of patients with asymptomatic or minimally symptomatic left ventricular dysfunction.

Some potential clinical applications of BNP is in the diagnosis of heart failure, a potential screening test for left ventricular dysfunction, and test for assessing ventricular remolulic following acute myocardial infarction.

Traditionally, the salt water was

regulated through the renin angiotensin aldosterone system converting angiotensinigen to angiotensin 1 and the lungs convert to angiotensin 2 which in turn stimulated aldosterone secretion that is responsible for salt water reabsorption thus increasing the blood volume.

Since the discovery of BNP produced by the ventricles of the heart has a negative effect on the angiotensin 2, it also has a negative effect on aldosterone and a negative effect on renin, thus promoting natriuretic and dieresis, thus decreasing the blood volume and the load on the heart.

Heart disease, if you divide it up, roughly 25 percent of all heart disease is congestive heart failure, 22 percent myocardial infarction, the other 28 percent coronary artery disease, and the other 25 percent being dysrithemias and other ischemic disorders.

Generally 75 percent of hear failure starts out with hypertension. Hypertension can result in myocardial infarction or left ventricular hypertrophy in which you get the left ventricular remodeling. These two diseases can progress to systolic dysfunction, diastolic dysfunction which eventually will lead to heart failure and ultimately

death.

The triage BNP test is part of an assay system. The system consist of a small fluorometer which is about the size of a telephone and a diagnostic test device that contains all the immunological reagents to perform the test.

Currently there is one product on the market that uses this format and that is the triage cardiac panel which measures and simultaneously quantifies myoglobin CKMB antriponin I and that is the picture we have here.

The test is performed as follows. Step 1, a few drops of blood are added to the device. The device is inserted into the instrument. The instrument takes the device into the instrument, determines when the test is completed, and displays the results on LCD and the operator has the option of printing the results to obtain a hard copy. The system can also be interfaced with the laboratory information system to coordinate the results with patient billing and so forth.

Clinical studies for BNP were several fold. First we wanted to determine the concentration of apparently healthy individuals, current concentrations in patients with nontreated

hypertension, determine the concentrations in the four classifications of the New York Heart Association for the stages of heart failure and look at the potential clinical use in clinical practice.

The clinical study sites were Hartford Hospital in Hartford, Connecticut, University of Maryland in Baltimore, University of California, San Diego, VA Medical Center in San Diego, Albany Medical Center in Albany, New York, and Biosite Diagnostics.

The four stages or four classifications of the New York Heart Association are Class I where essentially these patients are asymptomatic and have some left ventricular dysfunction; Class II, they are mildly symptomatic upon exercise; Class III, they are significantly symptomatic on exertion but are asymptomatic at rest; and Class IV, they are symptomatic in the resting stage.

The use of the New York Heart Association classification is very suggestive. It's going to be dependent upon each individual looking at the patient but provided us a way to stratify the patients in the different classes to where we can do some statistical analysis.

The overall advantage of using the New York Heart Association classification is you can

visualize as the concentrations increase with the severity of disease you cannot classify a patient into a single class. In other words, if a patient has a concentration of 2,000, he is not Stage I. If he has a concentration of 100, he is not Stage IV.

The potential uses of this product are to aid in the diagnosis of congestive heart failure. Another one would be to aid in the diagnosis and management of patients with congestive heart failure, but nonetheless the point-of-care test for the diagnosis and potential management of patients with congestive heart failure.

If you look at apparently healthy individuals, the concentrations range from zero or less than sensitivity of the assay up to about 400 nanograms/mL -- picograms/mL. I'm sorry. The hypertensive patients, as you can see from this particular diagram, the normal went up to approximately 100 nanograms/mL, the 95 percentile being somewhere around 40 or 50 picograms/mL and the hypertensive being significantly different.

I must note at this time the hypertensive patients Class I, Class II, Class III, and Class IV are significantly different populations from apparently healthy people using a Wilcox rank sum

test.

This is the distribution of BNP concentrations as a function of sex. As noted here, there is a significant difference between the BNP concentration found in men and found in women. Generally the median and the 95 percent confidence limits are higher in women than in men.

This actually depicts the numbers showing the median for women is 12 nanograms/mL, whereas the median for men was approximately five nanograms/mil, the median 20 versus 10, the 95th percentile being 57 picograms/mil versus 30 picograms/mL and, thus, all the other parameters are elevated.

If we consolidate the men and women, the overall median is about eight picograms/mL, the median being 16 picograms/mL, and the 95th percentile being 50 picograms/mil.

If we look at the BNP concentrations in Class I versus Class II, the New York Heart Association, we can see that some of the patients has concentrations that were within the normal range but there is a significant amount of overlap between CHF Stage I and CHF Stage II. However, CHF Stage II is also higher than the CHF Stage III when looking at the mean and the median.

Summarily, in comparing Class II and Class III, there is some overlap of these two classes but, again, CHF Class III, the mean, the median, and the 95th percentile is also higher than Class II. Lastly, comparing Class IV to Class III, there is some overlap with Class IV being much, much higher than that of Class III.

Therefore, the expected values as presented in the package insert of the product will provide the expected values between normal or apparently healthy people, hypertensive people, and the various four stages of the New York Heart Association going from eight picograms/mL to a median of 11 to 83 to 233 to 459 up to 1,024 picograms/mL. So using this stratification you can see as the severity of the disease progresses, so does the median concentration.

Looking at the relative sensitivity and specificity of these tests, I consolidated the apparently healthy people with the hypertensives because the hypertensives were not classified in the New York Heart Association classification of heart disease and they did not have heart failure. Therefore, I considered them to be true negative patients.

Sensitivity and specificity using a 40 picograms/mL cutoff or 92.8 percent or 93 percent and 89 percent respectively increasing the cutoff to 55 picograms/mL, the sensitivity remained essentially the same, 89.2 percent versus 93 percent going to 80. If the sensitivity dropped off to about approximately 84 percent, the specificity increasing to 95 percent going to 90 about 82 percent nsitivity decreases as one would expect in all age groups. The average sensitivity also decreases in going from 40 to 100 from 88 to 74 percent.

Likewise looking at the specificity in these same age groups, increasing the cutoff from 40 to 100 the specificity increases from about 74 percent up to 90 percent average depending on the age group and the number of patients.

At this time I'd like to introduce Alan Maisel who will provide you with some of the experience that he has had in using BNP in the evaluation of his product in his hospital.

DR. MAISEL: Thank you, John. I would like to thank the panel for having me here today. I would first like to reiterate I'm in San Diego. I'm a Professor of Medicine at UCSD and I run the CCU and in the Heart Failure Program at the VA. I got to know

Biosite because I had an algorithm that I was working on for a CCU diagnosis of heart attacks and I've been using their panel now for two years with very successful results.

About a year ago they asked me to look into a point-of-care test for peptide for heart failure. As anybody here who deals with patients and heart failure, we know it can be a terrific problem in diagnosing heart failure as well as managing heart failure.

While a big advocate of the neural-humoral hypothesis of heart failure, some of the neurohormones that we would measure to diagnosis or manage patients with heart failure are very difficult, take a very long time, and have a lot of overlap in values.

At first I was skeptical of testing a point-of-care peptide but that was about a year and a half ago and I will try to, seeing I'm in front of a very distinguished panel, unbridled enthusiasm and just present some data. I'll present data that has to do with the emergency department diagnosis of heart failure, the echocardiograph assisted diagnosis of left ventricular dysfunction.

I have also done work this past year in taking care of patients in the intensive care unit

decompensated heart failure using BNP levels. If any questions come up, we could talk about that. I've also used BNP in an approved protocol in my heart failure clinic for the last year and a half and I'm very, very impressed with what it can do there.

There are 400,000 new cases of heart failure every year. In fact, it's the most frequent cause of hospitalization in the elderly with almost 1 million hospitalizations per year. According to HCFA heart failure is a single disease where the most effort is spend trying to achieve cost effective management.

Because patients with left ventricular dysfunction have improved survival on our newer medications such as ACE inhibitors and beta blockers, it's imperative to make a correct diagnosis. This is especially true in the emergency department where a misdiagnosis in the emergency room could lead to incorrect treatment which would place a patient at additional risk for both morbidity and mortality.

Unfortunately, the signs and symptoms of heart failure are not very sensitive. Dyspnea, or shortness of breath, may be very unspecific in elderly patients or obese patients. Echocardiography has limited availability in emergency departments. It is

costly and it may not even reflect a cardiac cause for shortness of breath.

What we did in this pilot trial, we examined 250 patients who came to the emergency department with acute shortness of breath. They sign a consent for the study and we recorded data that had to do with the history, physical exam findings, and any laboratory tests that were ordered.

We asked the emergency department physicians to make an assessment as to their diagnostic probability that this patient with acute shortness of breath had congestive heart failure. BNP values were recorded but obviously blinded from all involved.

Later we took those forms. We had two cardiologists independently assess that patient for the diagnosis of congestive heart failure. We tried to develop as good a gold standard for the definition as we could.

In other words, with two cardiologists we had access to any tests that were ordered down in the emergency and any tests that were ordered as an outpatient. In other words, a patient might have had an echocardiogram ordered but didn't get it until two weeks later and we would have access to that. We

would have access to the hospital and the response to treatment.

So using generalized Framingham or NHANES criteria, we were able to come up with what we would say did this patient have heart failure as a cause of their dyspnea or did they not. The cardiologist, of course, also blinded to BNP levels.

Now, I'm going to show the data just in picograms/mL. In the manuscripts we have logged transformed data because it is a neurohormone so the population is a little skewed. But for presentation not knowing the scope of people in the audience, I'm going to just show it with standard errors and picograms/mL.

The first thing to show you is the huge differences in people that it did not have a final diagnosis of heart failure versus those that did; 38 picograms versus over 1,000. So this is a fairly overwhelming difference that we saw here.

Interesting enough, this middle group here were 14 patients who had known heart failure in the past. Several were in our own clinic so they had baseline LV dysfunction but their shortness of breath was deemed to be caused by something else other than heart failure such as pneumonia, bronchitis, COPD

exacerbation. As you can see, their levels while higher than the people who didn't have heart failure were again nowhere near the patients that came in that had acute heart failure as a cause of their dyspnea.

DR. ROSENBLOOM: What was the number in parenthesis?

DR. MAISEL: I'm sorry?

DR. ROSENBLOOM: What was the number in parenthesis? Was that the low?

DR. MAISEL: The number in parenthesis is --

DR. ROSENBLOOM: Is that the standard deviation?

DR. MAISEL: That's the standard error.

DR. ROSENBLOOM: Standard error?

DR. MAISEL: Yes, sir.

There were four panels on this slide that had to deal with our emergency department patients. On your upper left you see we have scope BNP levels in relationship to how the severity of the heart failure as per the cardiologist.

As you can see, which will correlate with data you saw previously by John Bruni, the more severe the heart failure, the higher the BNP levels. Patients who were admitted to the hospital on the

upper right also had higher BNP levels than those that were not admitted. Of course, those that were admitted with heart failure had higher BNP levels than those not admitted with heart failure.

I think that one of the most interesting clinical points to me are on these lower two panels. As a cardiologist, you know, we are supposed to be very good at diagnosing heart failure and we sort of say we are to the medical students and the residents. In fact, it can be very, very difficult for somebody who comes in and they are very, very short of breath.

The biggest reason we have problems, especially in our VA population where we have a lot of people with lung disease, is to separate lung from cardiac disease. Here we took the patients who had a final diagnosis of lung disease versus congestive heart failure and, again, a greater than ten-fold difference.

Finally, another common problem we see in the emergency department is people that came with shortness of breath but also had edema as a feature. In patients who had these two things but found out not to have congestive heart failure, there is their BNP level versus those that had shortness of breath and edema and congestive heart failure as a final

diagnosis.

This is a univariate analysis of signs down there that were recorded by ED physicians. I was happy to find that they correlated pretty much to what we see in the literature. There are certain things that are good if they are specific like JVP, rales, wet sounds in the lungs, third heart sound, but not all that sensitive, hence making the accuracy of the signs and symptoms of congestive heart failure in the emergency room not what we really need it to be.

This is just a univariate analysis of BNP levels in the emergency department. I started to use basically a cutoff of 80 going up to 150. You can see how accurate BNP was in this setting with a very high negative predicted value which is so important down there in the emergency department.

This is a multivariate analysis using a stepwise logistic regression. At the top what we did is we left BNP out until the end and then asked which features would be important to the physician, which came out to be significant in their assessment of the patient of having heart failure or not.

As you might expect, the history of heart failure would be very important. Heart size, murmurs, pulmonary-venous hypertension on the chest x-ray,

atrial fib, pedal edema. Those are the things that came out significant.

After that was all done, the best that they could do, the history, the physical exam, and any lab test BNP still had its significant information put in at the end to what anything else that they could have and taking accuracy up from 89 percent to 97.

This was also clear in patients where they came in without a previous history of heart failure which sometimes makes the diagnosis even more difficult. You can see here after logistic regression was done BNP still had a significant influence on the diagnostic accuracy of congestive heart failure.

Here is ROC curves. The emergency department, and I always have to say this first when I present this data because I don't want to make them think that they cannot diagnose heart failure. In fact, they did pretty good in this study. The lower ones, their ROC curve not having BNP and they were about an accuracy of about 88 percent.

In this study BNP -- and those are just a couple of the cut points. You see 80 up there and 205 -- had an accuracy about 97, almost 98 percent under the curve for the diagnosis.

It turned out that there were 30 patients

that were misdiagnosed by the ED physicians and it turned out in 15 they had over diagnosed it and 15 they under diagnosed it. We went back and we looked and we said what was the BNP there. In the 15 where they said this was heart failure they sent the patient out in many cases on heart failure medicines. Some got scheduled for cardiac catheterizations.

I could spend a whole hour telling you about these 30 patients because I've looked at them in great detail. The bottom line was that had they had the BNP concentration and used a cutoff of 80, you can see the mean BNP of those patients were only 46 if they had had those.

On the other hand, patients or physicians who sent patients home with the diagnosis other than heart failure, if they had the BNP level, they would have seen that the mean BNP level in this group was very high. In fact, 29 of these 30 misdiagnoses would have been corrected had that BNP level been available. As a cardiologist, you know, I had to follow up. I felt ethically bound once we finished the data to follow up on these patients.

As an aside, I must say it was absolutely amazing that we had our people in our system, and people have told me in other systems, that have been

filed sometimes for years with severe lung disease even though the pulmonary function tests are not all that abnormal and, hence, they have these BNPs and they finally get around to get an echocardiogram and their rejection fraction is now down to 10 percent or they have subsequent myocardial infarctions. It was a very, very eye-opening experience.

We are following up on this study in two ways. First of all, we are going to confirm this was an international multi-center trial. Secondly, we are starting another study in our emergency room right this week where half the time the ER physicians will have the BNP level and half the time they won't. Then we'll see what happens. I think that will really show the tremendous value.

I'll tell you, as a clinical practicing cardiologist, the hardest patients to take care of and diagnose down there are the ones who are the sickest who come in very, very short of breath and you have to move quick. The fact that you can get a level back in 10 to 15 minutes and have that be so valuable to me is just terrific. Our ED people don't even want to do the half-blinded now. They all would rather just have it themselves.

I want to talk a little bit about

echocardiography. I want to just read something that I found just before I got on the plane. I was going through my journals. Every month I get to go through a backlog that I didn't read for two or three months. I found the American Heart Journal for this month and there's an article called "Efficient Utilization of Echocardiography for the Assessment of Left Ventricular Systolic Function."

They start out by saying that unnecessary tests and procedures account for about 1/6 of the 1 trillion health care costs in the United States. One of the fastest growing tests in health care, and definitely the fastest growing in cardiology, is echocardiography. It is estimated that more than 15 million echocardiograms were performed in the United States in 1997 alone. In San Diego that's now about $750 to $800 a shot.

Well, not only that, besides being expensive we can't always get it when we want. We can't get it in our clinic. We can't get it in the emergency department. A lot of people think echos are the panacea but, you know, it can be pretty hard to get a good ejection fraction. People that are obese or have a lot of lung disease, they can be very, very hard to visualize.

Well, we were hoping that perhaps BNP levels could serve as an additional diagnostic blood test in patients who are referred for echocardiography for evaluation of left ventricular function.

So what we did at our VA, and I'm going to talk mostly about 200 patients but we've looked at our whole echo base and now it's well over 300 patients, but these 200 patients are patients that were referred for echocardiography at our hospital who did not have any known history of heart failure, who did not have any previous echos or any previous measure of ejection fraction but were referred because they wanted to know what their function was.

Now, about half of these patients had symptoms of heart failure and the other half did not. I should also mention that about 3 percent of every person walking around over the age of 45 has left ventricular dysfunction and about half of those are asymptomatic. We know now from studies even done by members of this panel that early treatment is essential to prevent onset of symptoms and progression of dysfunction.

There has also been some data not complete validated by other studies that suggest early on in the early LV dysfunction the natriuretic peptide

system actually be activated even earlier than the renin-angiotensin system which is maybe a way that you can help pick up some of these patients early. These were the 200 that we looked at.

Just to go right where the money is because I've already shown you what a big difference there was in the ED in people with shortness of breath, we ended up having a pretty good distribution. There were 106 who ended up having normal function and 94 who had abnormal. I'm classifying abnormal as either systolic or diastolic dysfunction and get into the definition of diastolic.

Diastolic dysfunction may be a third of all the heart failure causes and we don't really have a good way to diagnose it except by echocardiogram and those features are not by any means right now a gold standard. You can see again a ten-fold difference in our population.

We broke that down into people with decreased ejection fractions and also in people with diastolic dysfunction. In this group of patients since we only had 42, I didn't particularly go into the two different kinds of diastolic dysfunction which would be the restrictive or the impaired relaxation which were are going into in some other data, but by

general accepted criteria with Dr. Tony DeMuria at our institution who is a world echocardiographic expert we set this up.

Then finally patients who had a combination of systolic and diastolic dysfunction. This, by the way, is one echocardiographic feature that has the worst prognosis for patients with heart failure, systolic dysfunction. In this case we used short deceleration times to predict high wedge pressures, high left ventricular and diastolic pressures.

Interestingly enough these patients had very, very high BNP levels.

Here is the ROC curve. Again, the area in the curve here is about 94 percent. This is an earlier one. Since we are now writing all this up, we've gone up here into the 30s and the 40s where you get higher sensitivities.

I think this data conforms pretty much to what you've seen in the past where you have accuracy of tests that are 90 percent and above. I think that is very important. The interesting thing here I haven't really broken this down. I just took all abnormal patients.

Now, all abnormal patients could also

include patients that had a normal systolic function but had had a small little heart attack. I had to count them as abnormal. In fact, their BNPs were actually sometimes just in the high/normal range. Also some people with just small amounts of what we would call diastolic dysfunction.

I think as I break this data down further, it becomes more clear that the more dysfunction they had, systolic dysfunction or diastolic dysfunction, the more accurate these tests are at picking this up.

One interesting thing here when we talk about possibility of a adjunctive diagnostic test, this is a breakdown in people who had normal heart function and who had abnormal heart function. As you can see, the people that had abnormal heart function were a little bit older than those that didn't.

As you might expect, these people had a little higher incidence of hypertension, higher incidents of diabetes, more coronary disease, more symptoms, and a little bit more edema. You can see those don't help you that much because you see those frequently in both groups of patients.

However, you look at BNP levels and there is only 3 percent of our patients with normal function that had BNP levels greater than 80 and 85 percent of

abnormal. You can see how that test seems to segregate patients compared to what we normally use to help stratify patients as per risk.

Now, this is just at our institution. This is the distribution of patient referral that we get for echocardiography for left ventricular function. This excludes patients who they asked us to do an echocardiogram to look for a vegetation on a valve or to look for a source of a clot when somebody had a stroke. These are just our patients referred to for echocardiography.

About a quarter of them had known history of LV dysfunction. In those patients the mean BNP level was 798. The rest of our patient population, and I don't know if this represents the whole world because at the VA we get echos a lot. My friends tell me that everywhere they are getting echocardiograms a lot and they are using it in primary screening waves. At $700 a shot that's a pretty big deal.

It turned out that 76 percent of our patients referred for echocardiography had no known history of LV function. And in 106 of those where they had normal function by echo, again 40 percent of our patients had very low BNPs with only a few above 80. With an unknown history of LV function when they

ended up having an abnormal test, they had an abnormal BNP.

I think the conclusion there, we're not ready to -- I don't believe Biosite is necessarily seeking approval as a screening test. We're talking about diagnostic tests. Things that can help you in the emergency department. Things that can help you perhaps in the echolab whether you want to screen or, for instance, in our clinic now since we're studying this in an open way where we follow BNP levels every three months, that we always get an echocardiogram on patients with heart dysfunction because there's a lot of good use and I'm not trying to say we shouldn't do it.

We are actually able to follow patients very, very nicely now using every three-month BNP levels. If the patient's condition changes, the BNP changes. As we titrate medicine, the BNP can come down. We haven't needed to get these expensive echocardiograms very often at all and I think that has been very worthwhile.

I think for the future other things that we've looked at, and I can address if you want, is how to keep patients from being readmitted when they come into the hospital. We don't have good waves. We

don't know exactly how long to treat them and with what medications. In our experience BNP may eventually be very good as a neurohormonal modulator, if you will, if left ventricular dysfunction. Thank you for your time.

DR. BRUNI: Finally, to conclude the presentation, Biosite has shown that BNP can be used as an aid in the management or diagnosis of left ventricular dysfunction by the material submitted in the premarket approval and the PMA. Dr. Maisel has presented real-life cases in which it has been used in looking at patients in various stratifications.

Therefore, I would like to leave the panel with one message to where we can possibly go to. There are several intended uses we could have for the product to be used in the diagnosis of congestive heart failure used in the emergency department in the assessment of patients presented with dyspnea, independent assessment of left ventricular dysfunction. Also the literature supports that is the best predictor of morbidity and mortality in CHF patients.

Finally, intended use for the product could merely be an aid in the diagnosis of congestive heart failure, an aid to the diagnosis and management

of patients with congestive heart failure, or a point of care test to aid in the diagnosis and management of patients with congestive heart failure in the laboratory and the emergency department. Thank you.

DR. KROLL: Thank you. Before we open up for questions, we would like to ask if any of the people who just presented for the sponsor have any financial interest.

DR. BRUNI: I work for the company.

DR. MAISEL: I own no stock in the company and I received an unrestricted grant from Biosite to do my research.

DR. KROLL: Okay. I'd like to open it up to the panel members to ask the sponsors questions. We have until 11:00 to answer questions. Perhaps what we should do is go around the room and let each member of the panel ask any pertinent questions they have. We can start to my right with Nader Rifai.

DR. RIFAI: Just one clarification for Dr. Maisel. The study that you showed and the measurement of BNP was actually done in the emergency department or was done in the laboratory?

DR. MAISEL: For this study we did not give them the results and we did it in our laboratory but we did it right then. We have since then, and I

think John wants to talk about it, we have had regular physicians do it, regular nurses do it, regular technicians do it. In fact, the person who does it in my laboratory is a physician who is working.

DR. RIFAI: But not for this particular study?

DR. MAISEL: This particular study the blood was taken up as soon as we got it. One good thing is unlike other tests where we -- you know, when you're measuring cardiac neurohormones, it can be so hard because a lot of times you have to have the patient lying down for a half an hour and then you have to put it on ice and then spin it down and freeze it right away.

For this test it's sort of stable sitting out there for up to four hours so we'll run it within that time. If it's on a weekend or at night, then we can just spin it down and we get the same results if we run it. In the emergency room we did not put the machine down there but they want it down there.

DR. RIFAI: One of the problems you mentioned about diagnosing patient with congestive heart failure is to differentiate between those with congestive heart failure and those with cardiopulmonary disease. Were you able to see if BNP

helped differentiating between the two groups?

DR. MAISEL: Yeah. I think there was one of the panels where it showed that there is probably about a ten-fold difference if you just have lung disease versus you just have heart disease. There is a little bit of an overlap. If you have severe lung disease and if you have something called corpulmonalie which would be right ventricular enlargement, you can get a little bit of release of BNP there.

Those usually aren't presenting with acute shortness of breath. They usually often present with some exacerbation of their lung disease, but also a lot of edema. We are looking right now and we believe that BNP can separate adult respiratory distress syndrome from patients with heart failure. Those are people who come in with wet lungs and the x-ray looks -- you can't tell the difference. It's pulmonary edema but it could be cardiac or noncardiogenic.

Right now you have to put a catheter in the heart to differentiate that. A low filling pressure means it's ARDS. High filling pressure means it's cardiac. Well, BNP reflects basically a high filling pressure. In some early studies we've done it looks like it really is good to differentiate those two groups.

DR. ROSENBLOOM: No questions at this time.

DR. HENDERSON: I have a couple of questions. One, when you compared the groups, you have listed the standards errors. Any confidence intervals?

DR. MAISEL: Yeah. We have --

DR. HENDERSON: The numbers are relatively small in each group.

DR. MAISEL: Yeah. It's in our manuscript. I'll see if I have the manuscript here. We reported confidence intervals.

DR. HENDERSON: Okay. What I read in what they sent us, I don't think I saw that.

DR. MAISEL: It probably wasn't sent out. If you want, I can -- I'm pretty sure I have the manuscript here and they are in the tables there. They are pretty good confidence intervals.

DR. HENDERSON: The list of drugs when I read the document, did you look for any illicit drugs, cocaine use in patients? Was that ever a concern?

DR. MAISEL: In our particular patients only if it's indicated. I think obviously when we get patients who come in with chest pain and shortness of breath, then that usually triggers a drug panel.

It should be said that when these drugs do seem to interfere, it's a small percent interference rate and it does not appear to go to the really high levels that we get when people come in with heart failure.

I think the one really good thing about the test, you know, if we were only able to find normals and the E to A of BNP level of 40 when they didn't have it and 70 when they did, then I could probably write a paper with a good P value, but clinically it really wouldn't be that useful. There are such huge differences here.

I think the fact that John showed data that true normals are somewhere between 10 and 20 and 30, then I think there is probably a range between 30 and 40 and 80 where things like some lung disease may come into play a little bit. Hypertension may come into play a little bit. Maybe some drugs in the system may come into play a little bit. It's not until that left ventricular filling pressure, the heart failure, occurs that then you really see it shoot up to really big heights.

DR. HENDERSON: Were any pregnant women included in your women?

DR. MAISEL: No, they weren't. I don't

think they will be.

John, you may want to comment.

DR. HENDERSON: Obviously I have an interest. Certainly with preeclampsia we end up getting echos and looking at women for early evidence of left ventricular failures. I was just wondering if any happened to have been pregnant.

DR. BRUNI: We have an interest in looking at the potential use of BNP and preeclampsia in toxemia pregnancy but, to my knowledge, there were no pregnant women included in this particular study.

DR. MAISEL: As an aside, the women who runs the BNP studies right now, she's a physician, an OB from Yugoslavia who got stuck here in the war and sort of liked it and is afraid to go back. Now she's been pushing us to do this study so we may accommodate her.

DR. HENDERSON: Thank you.

DR. BRINKER: Perhaps for a simple plumber like myself who does interventional cardiology, you can elucidate a bit more on the pathophysiology of BNP. I get the impression that it reflects high ventricular and diastolic pressure because it's made in the ventricle I thought I heard said.

It also may reflect structural remodeling

so if you have a heart that has been remodeled, is very large, has poor EF but may not have -- may be treated and may not have a high filling pressure or may not in general have a high filling pressure, how would this respond?

DR. MAISEL: Well, for a plumber that's a great question. It really is because it turns out that I think your hypothesis is exactly right. For instance, with infarct BNP goes up very early with myocardial infarctions. Depending on how much remodeling goes acutely will depend on how far that BNP level will come back down.

That has been shown in at least two papers now to be very much predictive of subsequent survival and subsequent ejection fraction as how far that BNP goes. BNP itself, you know, it's release from the ventricle, a little bit from the atrium, and a really tiny bit from the brain. Unlike AMP it's mostly released from the ventricle.

There is not as much sort of storage as there is of AMP so you don't get the burst release that you get with AMP, which I think is very important for a diagnostic marker because I'll tell you one other thing. AMP, for instance, when you exercise it goes way up real quick as to catecholes and this and

that. One good thing about BNP is it doesn't.

I didn't bring a slide but we've exercised about 30 patients with heart failure and it really doesn't go up a heck of a lot which is so important because our heart failure people have to walk from the parking lot to the clinic and if we want a stable marker for them, we need a stable marker. We can't have something that triples with exercise and this doesn't.

Now, BNP seems very closely related to the filling pressure of the heart and that would be that you see in systolic dysfunction and sometimes in diastolic dysfunction. Of course, I believe that the New York Heart classification basically reflects the same thing because most patient's symptoms are dyspnea that reflects high left ventricular filling pressures.

There are some patients that have big hearts that have small ejection fractions that have BNPs that instead of 300 and 400 that are 80 and 90. We have about five of those in our clinic. What characterizes each of those patients is just what you said. Each of those patients are New York Heart Class I.

Each of those patients if I had any resident interview them, they would never pick up the

fact that they had heart failure because they play tennis, they swim, they do whatever they want to do. They have big hearts and the ejection fractions are low.

We all know while ejection fractions correlate with morality, they don't always correlate with symptoms. BNP appears to correlate much better with New York Heart classification than ejection fraction.

DR. BRINKER: You said that you like this because it doesn't go up when you exercise. Presumably when you did exercise your EDP would go up. The question is how long does it take to up regulate the production of this and how good is it for very acute heart failure?

DR. MAISEL: Great question and we've looked at that a little bit. Our exercise protocol occurred. We drew blood before right at the end of peak exercise and then we did it an hour later. The Class IV patients that exercised were the only group that one hour later you started to see a little rise in their BNP. Not the normals, not the Class I and II.

I think that's reflecting why I don't think you're getting RNA turnover that quick, although

it apparently has a very rapid message. You're getting some release from somewhere. Maybe a little bit from storage granules. I don't think anybody knows. We do see it in those patients and that's our hypothesis where the LVDP does go up with exercise that you start seeing that an hour or two later.

Now, when patients come in the emergency department with acute shortness of breath and there is BNP at 1,000 picograms, I don't know how long it took to get there. By the time they come to the ER, those patients are high. I do know, however, at least in 10 patients, how long it takes to come down acutely.

What we've done now, and we've just reached our 10th patient, where patients that were admitted where we had catheters in their hearts so we could measure the filling pressure, the wedge pressure, we drew BNP levels every two hours as we treated them with nitroprusside or millerone and the BNPs come down extremely nicely and extremely quick.

We could see delta changes of somewhere between 60 and about 110 picograms/mL every two hours that we measured it. I'm not sure exactly what that is. Is it because it's not being synthesized anymore or is it because we are restoring renal blood flow, hence the receptors for BNP are able to clear it now.

That's unclear.

The important ramification of that is that one of the experts in decompensated heart failure who I spoke with at the ACC meetings, Lynn Warner Stephenson, is a very big believer that when we measure heart pressure we just pull the Swan catheter right out and that's it. She believes that you need the titrate therapy to keep it low and that's what were finding.

We are finding that once you get the appropriate heart pressure and that the BNP is at 700, well, if you keep going for another 12 or 14 hours, that BNP comes down a lot lower and we think, at least, the patient may do better with that.

DR. BRINKER: One final question.

DR. BRUNI: Dr. Brinker, one thing they haven't looked at the correlation between the induction of the synthesis of BNP. BNP, unlike some of the other neurohormones, is not stored in secretory granules and is turned down as needed. Insofar as there is about a 23 minute half-life, the correlation with exercise and the appearance in the blood may not be timed quite properly at this point.

DR. BRINKER: My final question for now is you made an impassioned plea that heart failure is a

major cause of mortality and morbidity and especially in the elderly. If I correctly interpreted Dr. Bruni's comments earlier about the specificity of the test falls off fairly dramatically in the elderly. Is that true?

DR. BRUNI: The specificity fell off. If we could go to slide --

DR. BRINKER: I was looking at slide 38.

DR. BRUNI: If you look at slide 82, which is one I had in case there were questions. 84. You can see the BNP and there is a slight increase with age. Although these patients did not have a diagnosis of congestive heart failure, there were fewer patients in the 60 to 80 range that were apparently healthy and not diagnosed with disease. That does not infer that they are not hypertensive or not being treated for it or have some occult disease.

DR. BRINKER: On your slide 38 if we took the proposed cutoff of 40 picograms/mL specificity in this age group is 37 percent. If we took it at 80, which is a generous one, unless you have some sort of sliding scale it's only 66 percent. Of course, there may be this co-morbidity but this would be a real big population that you would want to apply.

DR. BRUNI: The specificity here is

referred to as -- this is compared to apparently healthy people. We are assuming that the people in the 61 to 100 age do not have occult disease being there's no history of hypertension. They could have some occult disease and, as Dr. Maisel stated earlier, patients starting to exceed 45 years of age start having some sort of left ventricular --

DR. BRINKER: In my reading of your work, I thought that while there may be a little shade of increase in hypertension, that you pretty much can exclude that. You can cut that difference and that would be exceedingly important, it seems to me, to differentiate the hypertensives from the heart failure.

DR. MAISEL: We're looking at that and I think other groups are using BNP to look at that also. I think the specificity is a little lower because I think in older people your left ventricle gets stiffer and the mechanisms of that are being worked out, but you tend to get more diastolic dysfunction.

Whether that reflects real high pressures in the left ventricle is not completely clear and that's only a minority of patients, but clearly echo features of delayed or impaired relaxation of the heart goes up with age. So much so that now echo

criteria for diastolic dysfunction, as you know -- I mean, look at E to A changes and things like this. You take into account age and you use a different formula for that. I think it still has to be worked out in part.

DR. MANNO: I only have a couple of questions at this time. One, in the documents that we read before we came, you made a point, or the company made a point of saying that this could help the economy of diagnosis.

You also mentioned the cost of echocardiograms. How do you see deciding using a value like this with that middle group when you're going to move on to doing echos and the other things? Because in the document you say this is not a stand-alone test.

DR. MAISEL: I don't think it's a stand-alone test. I think eventually for certain population groups it may be a stand-alone test. I think in our own work it could have been. In our echo population it probably could have been a stand-alone test. We didn't use it that way. We didn't say, "You can't have an echo."

Now my group, after seeing the data group of cardiologists, is now saying, "We can't do this

many echos. Let's use BNP." It may come down to be a screen. If you've got a BNP of under 40 or so, in our study you did not have anything wrong with your heart. Maybe eventually it will be.

I think right now we're using it to not only confirm the diagnosis but then after that maybe you don't need to get echocardiograms every three and six months like some people do and just use the BNP levels to maybe guide treatment and not the echocardiogram.

DR. MANNO: You're basically saying we don't have all those numbers quite yet?

DR. MAISEL: Right.

DR. MANNO: Okay. Good enough. One other --

DR. BRUNI: Also it's not stand-alone testing. No in vitro diagnostic test can stand by itself and diagnose a disease and eliminate the expertise of the physician.

DR. MANNO: I agree with that. I just was trying to rationalize between the presentation and the written word because everyone will ultimately read the written word and do what they want anyway. At any rate, at the very outset you basically described three, the AMP, the CMP, and the BNP. In the actual

practice of the test running, how much contribution from the CMP and the AMP do you see in the end result?

DR. BRUNI: I don't have the PMA in front of me but in the PMA there's a specificity table in which we look at the activity of AMP and CMP with the BNP test and there was essentially no reactivity.

DR. MANNO: Okay. Thank you. That's all.

DR. KROLL: Let's continue with questions from the rest of the panel. Actually, we can go to Dr. Gutman.

MR. REYNOLDS: I just have a couple of very brief questions. I do understand that this test if primarily meant to be used as a point-of-care test. Is that correct?

DR. BRUNI: The test can be used both at the point-of-care and in the laboratory.

MR. REYNOLDS: Okay.

DR. BRUNI: We have provided some data to FDA of 10 health care professionals performing the test. These were nurses, doctors, and technicians with a masters degree in the medical field.

MR. REYNOLDS: Would it be used anywhere other than the hospital and you would see other than in the lab or emergency room like a coronary care unit or anywhere like that?

DR. BRUNI: It could be, yes. That's why we used health care professionals, nurses who would be in the coronary care unit and so forth.

MR. REYNOLDS: Did you take any look at all at testing where instead of a regular vena puncture a central line was used to draw blood?

DR. BRUNI: No.

DR. MAISEL: I actually have because with our patients we would often take it there and we get this sort of same little decrement. The first one where we tried it we would often compare. If they were doing a vena puncture stick the same time they put the CDP line in, we would take one at that time and it doesn't seem to make a difference.

DR. BRUNI: But the data will be brought up to date, though.

MS. AMMIRATI: I just have a couple questions. One is just academic and the first one that isn't which is on, I guess, slide 37. I was curious as to the number of ends in the various age populations. Not exactly but --

DR. BRUNI: I don't have it broken down with me.

MS. AMMIRATI: Okay.

DR. BRUNI: As the population increased,

if you look at slide 84, you can see as you get to the 60 to 80 range, or 60 to 100 the end number is actually much smaller.

MS. AMMIRATI: Right.

DR. BRUNI: That's going to count for the larger difference in specificity in apparently healthy people, especially for the fact we did not know if they had any sort of occult disease and they did not receive echocardiograms.

MS. AMMIRATI: If this number is somewhat dependent on the smaller population it's going to have artificial --

DR. BRUNI: It's going to have a larger negative impact. Yes.

MS. AMMIRATI: The other question is academic. From the normal population it looks like the women as a median or mean ran higher than the males. Is there any reason for that?

DR. BRUNI: We've looked at that. I've got a number of slides for showing the correlation, date of last menstrual period, phases of the menstrual cycle, and so forth, and we didn't notice a correlation of anything other than the fact that women were running higher than men.

MS. AMMIRATI: That's all.

DR. EVERETT: In the design of the device, what is the rationale for the two different types of antibodies used in the device? In one instance it seems that there's a combination of both monoclonal and polyclonal antibodies in the test.

DR. VALKIRS: The monoclonal antibody was obtained from the organization or the SCIOS company that licensed the product to us. We found that the existing monoclonals didn't give us as good a sensitivity as was necessary to get into the normal range of the patient population so we developed our own antibody and that antibody is a polyclonal antibody but it was prepared and selected by phage display. It's not a polyclonal antibody from an antiserum. It's a recommonate antibody that is reproduced and can be made from lot to lot with consistency.

DR. EVERETT: So which one is used in the device itself?

DR. VALKIRS: Both are used. One is used to capture the BNP on a solid phase and the other one is labeled with a fluorophur and that is what's detected by the meter.

DR. KROLL: Thank you for answering that question but could you please introduce yourself?

DR. VALKIRS: Oh, sorry. I'm Gunars Valkirs, the Vice President of R&D from Biosite.

DR. KROLL: Thank you.

DR. EVERETT: So my question then is BNP the same in males, females?

DR. VALKIRS: Yes, it is.

DR. EVERETT: And no appreciable difference in the detection limits or the ability of the test actually to measure?

DR. VALKIRS: No, it's not dependent upon the source of the sample. The BNP is the same.

DR. EVERETT: Okay. So it appears as though the sensitivity and specificity changes with age. Is that correct?

DR. VALKIRS: That's correct but I think John Bruni has already addressed some of those issues with the low end number and our lack of knowledge about those apparent normals above the age of 60. There may be occult disease there.

DR. EVERETT: Okay. Then I guess my other question then is the utility of the device itself. Were there any patients that you investigated -- I guess you did it with your emergency room patients -- that you systematically excluded from the study itself?

DR. BRUNI: The only patients that were systematically excluded from the study were those patients for which we could not get a complete history and complete diagnosis of congestive heart failure. There were approximately 100 or so that were unresolved and we continue to try to resolve the disposition of those patients.

DR. EVERETT: So the exclusion occurred at the beginning of the presentation of the patient or after you couldn't make sense out of the data?

DR. BRUNI: After we couldn't make sense out of the data but we included the patients with congestive heart failure. Once the data forms were tallied and so forth and we lacked an age or we lacked a stage of congestive heart failure or there wasn't a final diagnosis in the chart, we had to exclude those.

DR. EVERETT: And how many were excluded?

DR. BRUNI: Somewhere around 100.

DR. EVERETT: Out of a total?

DR. BRUNI: Of 1,012.

DR. MAISEL: In our clinical study in the emergency room we didn't exclude anybody once they were answered. We checked the ICD codes. We gave about eight ICD codes to capture everybody who came in the emergency room within that five-month period

including anybody in ICD codes with shortness of breath, lung disease, asthma, congestive heart failure.

We actually did a lot better. We got about 70 percent of anybody who came in with a code that could remotely be construed as possibly having heart failure so we were very happy with that.

DR. EVERETT: Okay. And I know you talked about this earlier but the rate of rise. Do you have any real data on the rate of rise of BNP?

DR. MAISEL: I think John Burnette from Mayo Clinic has some from some animal model study. I can tell you in terms of our clinic population. If someone comes in and tells me they don't feel good and then by the time they get to the emergency room, they are in pulmonary edema. Their BNP is already quadrupled to what it is in the clinic. I would suspect but we don't have the data.

DR. BRUNI: There are no experiments, to my knowledge, of people inducing higher preload pressure in humans to look at a rate of rise. As Alan said, there are some studies in dogs and so forth but in the human being knowing they are going to present with a disease and measure it and I don't know of any instances where they would induce a rise in the

pressure to try to see the rate of rise of BNP.

DR. EVERETT: So, again, where do you see it fitting in to the clinical evaluation of a patient who you see who you suspect may have congestive heart failure?

DR. MAISEL: I see it fitting in a number of areas. I see it fitting in right down in the emergency room. I think I showed you that data. I see it fitting in very nicely actually in the hospital. I think you are going to see that people as they remodel after an infract, some of those go on to develop congestive heart failure sometimes right in the hospital.

In those patients, we don't have a lot of them, but we looked at them and we see the BNP going up every day, I think, in the evaluation in the possible adjunctive diagnosis along with echocardiography. I believe also in the elucidation of diastolic dysfunction.

We don't know how to diagnose diastolic dysfunction. It's a third of all cases of heart failure. They have symptoms of heart failure but their squeeze is normal. They have a normal ejection fraction and they call it diastolic dysfunction but we don't know how to get a handle on it.

I think even someone from Columbia is doing some work on this. Since diastolic dysfunction is often associated with higher pressures in the heart. If you have a normal pumping heart and you have a high BNP level, than that should be diastolic dysfunction.

We are taking a look at that in a lot of patients as well as some other people are and trying to associate that with some of the known criteria. I believe down the road it's going to be a very useful adjunct in the diagnosis of not only systolic function but diastolic dysfunction.

Finally, I think in talking to cardiologists all over, people who run congestive heart failure clinics, they want to down the road use this in their clinics as titrate therapy because one of the biggest problems that we have, because there are so many good and new medicines out there, which ones do you put them on and how much do you put them on.

There are countless debates about how much ACE inhibitor a patient should be on. Where do you stop titrate? How much cartvatalol? How do you know if you can give them more of a certain beta blocker? These are our questions that we are dealing with in

clinic every day and we don't have any answers.

We know if we give them too much they get hypotensive and they get asymptomatic so we often stop short. Now there are some pretty good data and maybe Dr. Packer would comment on it. There's some pretty good data that suggest that higher doses may be better.

It turns out that we may be able to use this because BNP is, in fact, a measure of what's going on in the heart. It is a neurohumoral modulator and what we think is the neurohormones are now probably the biggest players in the progression of left ventricular dysfunction and ultimate poor prognosis.

I think in those areas to get them out of the hospital, perhaps to be able to titrate treatment in the hospital and then in the clinic because that's where we really want to keep, you know, 30 to 40 percent of patients readmission rate at six months after they get out of the hospital. We obviously need to do a better job and I think part of that we might be able to titrate medicines there with BNP levels.

DR. EVERETT: So the device is designed to tell me precisely what, the level of the BNP or the status of the heart itself, or if the patient is in

CHF?

DR. MAISEL: I think the device is designed to give you a level that needs to be interpreted with other things. In the emergency room I think for my ownself it can be extremely valuable as an adjunct for diagnosis. If you are about to send a patient out of the emergency room and you are sure that shortness of breath is asthma and that BNP comes back 800, you better not be sending that patient out because that is a 97 percent likelihood at that level to be heart failure and they miss a diagnosis. I think that is very clear.

DR. EVERETT: Thank you.

DR. CLEMENT: Another question, actually regarding the slide and some of the outlyers. I mean, you touched on some of the answers on it. Some of the patients were way outlyers. They have advanced age, 82. There's one patient that had a level of 336 and another was 385. The one that was 385 was 82 years old, for example. This is looking at the raw data on the sheets that were provided us earlier. The person that was 336 was 79 years old.

I know in a large population study like this you can't go back and do echos on everybody. Then you get inherent bias if you actually start

looking at individual patients that happen to be outlyers. I'm just curious from a clinical perspective. Was any follow-up done on those patients?

DR. BRUNI: No, the accuracy of this is dependent upon the accuracy of the physician recording the status of the patient and the information that the patient provided to the physician. There was no going back and looking at this. They could have had occult disease. They could have had high blood pressure that wasn't recorded.

DR. MAISEL: In our two studies, as well as what we've done in the hospital, we followed up on all those patients, whereas a new diagnosis that really wasn't -- you know, we're following a lot more patients because of that. Some of them, as mentioned before, were basically horrendous stories about people who had been followed for years without the diagnosis and they are now getting proper treatment.

DR. CLEMENT: I think another question -- it's more of a comment about this whole issue of what is it exactly measuring. I'm not a cardiologist but I work in the ICU and several years in training and also in ER.

It sounds like you are measuring a point

of left diastolic pressure without doing a Swan-Ganz by basically correlating -- I mean, to some extent based on your data I'm looking at LV EDPs. Would that be your sort of assessment of this, too, or is it more than that?

DR. MAISEL: I think it's more than that, although if it was just that, I think that would be great because we use way too many Swan-Ganz catheters if you could do without some of that, but it does reflect high left ventricular filling pressures.

I'm thinking it also reflects -- you know, when people come in with decompensated heart failure, we don't know what drugs to give them. Some people have said that you should never give a ionotrope, dobutamine, because in the long run you're going to get apoptosis and you're going to hurt yourself more than not, or your milleron is not very good.

We really haven't had a way to judge except we do something to get the wedge pressure down. We've looked at about 40 of those patients right now just with Swans in and then sort of follow them 30 days out and it really looks like that it's not short-term treatment. From this 40 patient data it is not going to be affected by giving an ionotrope if you get that BNP down to a reasonable level.

It's not just the wedge pressure because what we've seen, and this is exactly what Lynn Warner Stephenson is testing in this new study where they get a Swan or no Swan in the escape trial, is that once you get the wedge down to 17 and you say, "Okay. We've done our job. Put him on oral medicine. Take it out and send him back," it's not enough.

What she says is it's not enough and what we see is that the BNP the next day after it reaches 17, when you continue that nitroprusside, when you continue millerone, it continues to fall and fall and fall. I think that's when people talk about the neurohormonal hypothesis and how the neurohormones are up when the heart failure gets bad.

We've never had a way, sort of point-of-care, to measure how they are demodulating so I think it is a little bit more than just a Swan but it needs to be proven. I think a lot of people, and I could tell from the last heart meeting, are considering in any multi-centered trial that they are doing this want to use BNP to gauge therapy.

DR. CLEMENT: One last question. Would you like to comment a little bit more about the specifics of this slide 51, the 30 misdiagnosed patients which I think is extremely fascinating.

Clinical scenarios I can suspect is someone that may have acute bronchitis and may have a little touch of heart failure and trying to decide in the ER situation.

DR. MAISEL: The cases I can just tell you because I have a litany because I've looked them all up. I have slides with case studies of about seven of them just to illustrate to our house staff what, you know -- wow. If for nothing else because they can't really use BNP yet, but if for nothing else to say pay attention.

Don't go by chart lore. That means they see that the patient's a smoker and has a history of lung disease and that's it. They are never going to get the diagnosis of heart failure. Most of the cases where they miss heart failure they had underlined lung disease. Some did but a lot of them sort of were called to underline lung disease and did not.

Where they said it was heart failure and it wasn't, it was for any of a number of reasons but a lot of times they had some corpulmonalie and maybe they had a little bit of edema. Really once we saw that their pulmonary function tests were terrible or a bronchodilator helped them and their EF was good and they didn't have any diastolic dysfunction, then he

probably doesn't have heart failure.

These were egregiously clear unfortunately, I think, in a way. I mean, fortunate for the test but unfortunately for the house staff down in the emergency department. It means that you have to take a better history and do better physicals.

DR. CLEMENT: Well, I think, as you said, the diagnosis for this table was made retrospectively after seeing if they responded to treatment.

DR. MAISEL: Absolutely. That's because we needed to get a good gold standard and that was the fair way to do it. In the next study now we are going to actually -- half the time they will have the BNP 15 minutes after the patient comes in and consents. Then we have scales to see what they are going to do with that, how confident they are, and then we'll compare. Then if these get corrected, I think, then that will make the answer.

DR. CLEMENT: Okay. Thank you.

DR. PACKER: All of the data that we have that's been submitted to the panel on specificity, sensitivity, the shape of and the specifics of the receiver operator curves are based on this selection of the control group and the patient group in the data submitted.

I have concerns about the selection of both the control group and the patient group. The average age in the control group is 42 years old. The average age of heart failure in the community is about 70 to 73. The average age of your own heart failure group was 66.

This is a hormone that increases with age so that I'm curious as to how you think we can use your control group to construct sensitivity and specificity curve calculations or receiver operator curves if this is a control group which is not age-matched. You said in your protocol you wanted an age-matched group. You didn't achieve an age-matched group.

DR. BRUNI: It was very difficult to attempt to achieve an age-matched group in patients exceeding 50-60 years old who were not taking some sort of anti-hypertensive. In most of these hospitals the clientele appearing there were not apparently healthy people to where we could achieve that. If you look at both populations, the control group appears to be skewed to the right, whereas the experimental group appears to be skewed to the left.

DR. PACKER: I totally agree that it's very hard to get a control group but it's very

important to get a control group.

DR. BRUNI: But also if you look at the various cutoffs from 40 picograms/mL up to 110 picograms/mL there's very little change in the sensitivity and specificity of the test.

DR. PACKER: If you go back to the number of patients you have that are over the age of 65 in your control group, it's very small.

DR. BRUNI: Very small, yes.

DR. PACKER: I don't know how you can use that as a control group if I see patients and Alan sees patients with heart failure and they are in their 60s, late 60s, 70s, 80s. This is a disease of the elderly. This is not a disease of the young. Very few people with heart failure are 35 or 40 or 45 years old.

Very few people with heart failure have an age similar to your controls. I don't know how to calculate specificity and sensitivity. I've seen the breakdown based on age that you've shown but that breakdown is based on unbelievably small numbers in your control group.

DR. MAISEL: I can't speak for the statistics on the PMA but I can tell you in our papers that we're writing up. For instance, in our ER

population the guys that had heart failure and didn't have heart failure, in other words had pulmonary disease, the average age was about 60 in those patients in both groups.

Again, I do believe in our experience I have probably run BNP samples on about 3,000 patients for studies and probably about a quarter of those are no significant LV dysfunction. In the studies in the emergency room, I do believe the BNP goes up with age. I don't think it goes up in age past about 60 to 70. I think --

DR. PACKER: But how do you know? There's preciously little data in the cohort which is comparable to the cohort in patients with heart failure. As Steve was saying, you have outlyers that are old that have high BNP levels. I don't know if they are outlyers. That might be what patients who are elderly have for BNP levels. That's important to find out.

DR. MAISEL: I agree with that. I could say from our data from our hospital but I can't speak to what John has said. Some of our outlyers indeed in the emergency department weren't outlyers. When we went back and looked, those guys had congestive heart failure and so it's possible that if somebody has told

you somebody is a normal patient and is old, then they could have CHF.

DR. PACKER: But, Alan, that's circular.

DR. MAISEL: Right.

DR. PACKER: You can't go there from here.

DR. MAISEL: But what I could say is that down looking at our patients in our studies down in the ED where they either have it or they don't, and the veteran population, the mean age is not 45, it's up in the 60s, that the average BNP level for all patients who did not have heart failure was about 46 picograms/mL. That is 100 patients whose mean age is 60 something or other. I think they probably did need more and just could not get it.

DR. PACKER: I mean, this in part may account for why women have higher BNP levels than men because women have more age related diastolic dysfunction than men.

DR. MAISEL: Absolutely.

DR. PACKER: That's very well established in literature. All that means is that there is a phenomena going on in the elderly which, to my view, has not been adequately explored in terms of establishing a true control group and a true range of values that can be used to construct specificity and

sensitivity curves.

Based on your own data, you've got values running around 37 to 66 percent depending on what you use for a cutoff. That's dramatically different than 90-95 percent if you use the data from a control group that is only 44 years old or 42 years old.

Let me ask a question about the patients who were actually diagnosed as heart failure. Protocol specifies that patients with a history of MI would be excluded.

DR. MAISEL: If they had an acute MI, they would be excluded.

DR. PACKER: Protocol said any history of an MI.

DR. BRUNI: That was a change in the protocol which I did not note in the copy you received. Patients that had a previous MI were included but patients presenting to the hospital with an acute MI were excluded.

DR. PACKER: Okay. Patients with a history of MI according to the documents that we have received represented only about 100 patients.

DR. BRUNI: Right.

DR. PACKER: One hundred out of 1,000 patients.

DR. BRUNI: Yes.

DR. PACKER: Ten percent of the population.

DR. BRUNI: Yes.

DR. KROLL: Please use the microphone.

DR. BRUNI: Yes.

DR. PACKER: That is a pretty atypical heart failure population. A large proportion of patients with heart failure have a history of myocardial infarction probably in the range of about 50 to 60 percent.

DR. BRUNI: In the particular cohort that we studied, that's the percentage that showed up. Out of that 1,000 patients 430 were apparently healthy individuals and there is 167 that were patients that were hypertensives so you're looking at roughly 100 out of 500 which is closer to 20 percent.

DR. PACKER: It's still a pretty atypical population in terms of just the kinds of patients we see. Let me ask a question. Is BNP renally clear?

DR. BRUNI: Yes, through the receptor on the kidney and also through a neuropeptidase present in the plasma.

DR. PACKER: Did you measure renal function in your patients?

DR. BRUNI: No.

DR. PACKER: Do you have any idea whether changes in renal function affected the specificity and sensitivity measurements since lots of people with heart failure have impaired renal function?

DR. BRUNI: Changes in renal function, no. We didn't correlate that but in a pilot study that I've been working on that is shown on slide 94, we looked at 70 patients prior to hemodialysis and patients going for hemodialysis for renal failure. It's noted that their median value and their 95th percentile is also elevated but not quite as elevated in CHF-I. This is a study that is ongoing.

DR. PACKER: So if a patient had a creatinine of 1.5 their BNP might be increased?

DR. BRUNI: I cannot say that because we didn't correlate it to the creatinine.

DR. PACKER: Lots of elderly people have creatinines that are in the normal range but they have greatly impaired renal clearances with are not reflected by their serum creatinines because of low body mass. How would one know what the specificity or sensitivity is in a marker which is renally cleared if renal function hasn't been measured?

DR. BRUNI: It's clear both renally and in

neuropeptidase. The primary mechanism is through the MPC receptor C which is located on the kidney and internalization. It's internalized into the kidney cell and metabolized as opposed to cleared renally.

DR. PACKER: Well, it seems to be increased in people who have impaired renal function.

DR. BRUNI: That probably could be due to the increased preload on the heart.

DR. PACKER: It could but it would be nice to know.

DR. MAISEL: I agree that it would be nice to know. There are papers out there that suggest dialysis patients have higher BNP levels and after dialysis the BNP levels go down. I think people are starting to look at that in terms of echo criteria for diastolic dysfunction.

I don't think when you have creatinines of 1.5 and 2 and 2.5 you don't see BNP levels go up greater than -- if they don't have heart failure they don't really go up greater than 100. What we do see in the patients that come in with decompensated heart failure and we put a Swan in and their creatinine is 3 to start with, I think it takes the BNP longer to come down. I think that is definitely true.

DR. PACKER: Let me ask a different

question. do you think that there is a correlation between BNP levels and ejection fraction?

DR. MAISEL: There is a known correlation between BNP levels and ejection fraction. It has been studied and published from Europe.

DR. PACKER: Can I ask you to look at the figure provided to us on page 278, Vol. I, and the associated figure on page 279. Our squared here is .09. Do you think there is a relationship between the ejection fraction and BNP level?

DR. MAISEL: Again, I wasn't particularly involved in this collection. I would want to know was it echo, was it nucleotide ejection fraction.

DR. PACKER: But these are the data in the application.

DR. MAISEL: No, I understand that. I think the best -- I spoke to that a few minutes ago and I think the best correlation -- other studies have shown that really low EFs have high BNPs. I think that if you broke down this data here, and remember you're looking on the X axis of zero to 7,000, I think if you took that low EF down below 20 and greater than 40, you would see something.

I think that is where most of the correlations are seen. I think BNP correlates much

better to symptoms and to New York Heart Class than necessarily ejection fraction. I told you I have five patients with poor ejection fractions and BNPs in the high normal levels, yet they're all New York Heart Class I. I would say that as long as that data method collection was good, then that's the data.

DR. PACKER: But, Alan, this figure is as good as it can get because if you cut it off at 1,000, this even looks a little bit better because there are a few people who have values of 3,000, 4,000, 6,000. If you cut it off at 1,000, which is sort of a pretty high level of BNP, there is nothing here.

Let me ask the question in a different way. Do you think this test can distinguish between systolic and diastolic dysfunction?

DR. MAISEL: No. I think it can distinguish between normal function and abnormal function.

DR. PACKER: The reason for asking is if you don't think it can distinguish between systolic and diastolic dysfunction, then it shouldn't correlate with ejection fraction because the biggest difference between systolic and diastolic dysfunction is ejection fraction.

DR. MAISEL: You're saying that might

explain the data and I haven't really had a chance to look at this particular data but it may be -- were diastolic functions -- I take it they were in here. If they had heart failure?

DR. KROLL: If I could interrupt for a minute. I think we would like to take a break soon. What I would like to do now is let Dr. Packer and Dr. Comp and myself ask some specific questions that we don't expect an answer right now but later on if you look at the agenda we are going to have open committee discussion. These are questions that we can bring up again. It might give you a chance to prepare some answers. Does that sound agreeable to you?

DR. PACKER: I think I still need some clarification on a few issues with your permission.

DR. KROLL: I mean, that's fine. We can clarify them later, too. We'll have time in the afternoon.

DR. PACKER: It's up to you.

DR. KROLL: Why don't you go ahead and finish trying to clarify the points then.

DR. PACKER: The only reason is I just want to -- I think it's important to the panel to get the sponsor's view on how they think the test should be used. In the area of heart failure we have two

kinds of patients who present in this instance.

There are patients who have no symptoms, and what we want to do is know what their ejection fraction is because we know that if their ejection fraction is low, we should treat them. If their ejection fraction is normal, they don't require therapy.

In patients who are symptomatic, what we want to know is there ejection fraction high or low because if their ejection fraction is low, we have treatment for low ejection heart failure. If their ejection fraction is high, the treatment for heart failure is totally different.

Treatment for heart failure depends on the ejection fraction more than it depends on anything else whether patients have symptoms or no symptoms. I just want to understand if the patient doesn't have symptoms, this test can't detect a low ejection fraction. Is that right?

DR. MAISEL: In our studies of echos, about half the people had no symptoms at all and were just in for a screening and it still picked it up.

DR. PACKER: But you said there is no relationship with ejection fraction so it's not a screening test for low ejection fraction.

DR. MAISEL: I said I'm trying to explain this figure to you and I have to go back and ask John where all the patients came from, whether this was all inclusive of people with heart failure because whether he collected people with hypertension and heart failure and some of these had diastolic dysfunction.

If that is the case, then that is the end of your question because that's the answer in this graph why you don't see that correlation. That I suspect is what happens.

I think if you look in the literature, there is correlation in people with systolic dysfunction. It's the same kind of correlation that you get between ejection fraction and New York Heart Class. I mean, it's not perfect but there is some correlation. The lousier it is the worse you feel generally, although you don't have to be. I think that's what we're seeing here. You see a better correlation with --

DR. PACKER: The only reason for bringing it up is that since what we want to do is be able to know who to treat and who not to treat and how to treat them. If a patient has symptoms, BNP isn't going to help you. You still need the echo because you still need to distinguish systolic from diastolic